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Relationship Between Bone Mineral Density and Biochemical Markers of Bone Turnover in Hemodialysis Patients

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ABSTRACT

End-stage renal disease is closely associated with changes in bone and mineral metabolism. In recent times, osteoporosis has become important among hemodialysis (HD) patients. In this study, the investigators sought to evaluate the relationship between bone mineral density (BMD) and biochemical markers of bone turnover among HD patients. A total of 70 uremic patients on a maintenance HD program for at least 1 y were enrolled in the study. All patients were treated with conventional bicarbonated HD for 5 h through the use of low-flux hollow-fiber dialyzers. Bone densitometry was measured by dual energy x-ray absorptiometry in the lumbar spine (LS) and the femoral neck (FN). BMD was classified according to World Health Organization criteria on the basis of BMD T scores. Biochemical bone turnover markers such as calcium, phosphorus, ionized calcium,

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intact parathyroid hormone, alkaline phosphatase, plasma bicarbonate, blood pH, serum albumin, and hematocrit levels were measured before the HD session in the morning. Male patients (n=37; 52.9%; mean age, 46.2±17.0 y) were assigned to a single study group, and female patients (n=33; 47.1%; mean age, 44.0±13.1 y) to another. Mean duration of HD treatment was 33.7±28.5 mo in females and 33.0±26.0 mo in males. Among all patients, BMD T scores in the osteopenia/osteoporosis range were observed at the LS in 58 patients (82.8%) and at the FN in 45 patients (64.3%). According to BMD measurements in FN T score, 10% of patients (n=7) were osteoporotic, 54.3% (n=38), osteopenic, and 35.7% (n=25), normal. On the other hand, in LS T score, the results were 47.1% (n=33) osteoporotic, 35.7% (n=25), osteopenic, and 17.1% (n=12), normal. No statistically significant association was found in osteopenia/osteoporosis between sexes according to FN and LS T score (*P*=.542, *P*=.267, respectively). No significant relationship was noted between BMD and biochemical markers of bone turnover. A positive correlation was found between FN T scores of BMD and age (*r*=.413, *P*=.000). BMD T scores within the range of scores for osteopenia/osteoporosis were observed in 78.5% of patients at the LS and in 58.5% of patients at the FN. The investigators concluded that no correlation could be found between markers of bone turnover and bone mass measurements in both skeletal regions. LS T score results were worse than FN T score results. Elevated alkaline phosphastase levels combined with high intact parathyroid hormone levels are predictive of renal osteodystrophy but not of adynamic bone disease/osteoporosis.

Keywords: hemodialysis patients; bone mineral density; biochemical markers

INTRODUCTION

End-stage renal disease (ESRD) is closely associated with changes in bone and mineral metabolism. Approximately half of patients exhibit signs of secondary hyperparathyroidism at the beginning of hemodialysis (HD); in one third of these patients, adynamic bone disease may be diagnosed.[1] In addition, because of advanced age, poor nutritional status, sedentary lifestyle, drugs such as immunosuppressants and steroids, inadequacy of hemodialysis, and chronic acidosis, these patients may be at high risk for developing osteoporosis.[2,3]

In recent times, osteoporosis has become more important in the HD population.[4-6] Although it is known that the double-labeled tetracycline biopsy is the gold standard for diagnosis of adynamic bone disease, it is invasive and is associated with practical difficulties. Therefore, new techniques and biochemical markers are under investigation for the diagnosis of adynamic bone diseases, such as osteopenia and osteoporosis.[3,5]

In this study, the investigators sought to evaluate the relationship between bone mineral density (BMD) and biochemical markers of bone turnover.

MATERIALS AND METHODS

A total of 70 uremic patients who were on a maintenance HD program for at least 1 y were enrolled in the study. All patients were treated with conventional bicarbonated HD for 5 h 3 times per week with the use of low-flux polysulfon hollow-fiber dialyzers (Fresenius Medical Care, Bad Homburg, Germany). BMD was measured in the lumbar spine (LS) and the femoral neck (FN) with the use of the Hologic DEXA system

osteodensitometer (Hologic QDR–1000, Bedford, Mass). BMD was classified according to World Health Organization criteria: T scores within 1 standard deviation (SD) (+1 or –1) of the young adult mean were accepted as normal, those 1 to 2.5 SD below the young adult mean (–1 to –2.5 SD) as osteopenia, and values 2.5 SD or more below the young adult mean (≤–2.5 SD) as osteoporosis. Blood samples tested to assess biochemical bone turnover markers were collected before the HD session in the morning.

Biochemical bone turnover markers such as calcium (Ca), phosphorus (P), and alkaline phosphatase (ALP) were measured with the use of routine biochemical procedures performed on the Aeroset/C8000 autoanalyzer (Abbott Diagnostics, Abbott Park, Ill); intact parathyroid hormone (iPTH) was detected through 2-site chemiluminescent enzyme-labeled immunometric methods with the use of DPC Immulite 2000 (Diagnostic Products Corp., Los Angeles, Calif). Plasma bicarbonate (HCO_3), blood pH, and ionized Ca levels were assessed in heparinized arterial blood with the use of the radiometer ABL 735 blood gas analyzer (Radiometer Ltd, West Sussex, UK). Complete blood counts were measured on CELL-DYN 3700 (Abbott Diagnostics). Urea clearance time × dialysis time/volume (Kt/V) values of all patients were calculated with the use of the Daugirdas formula. Male patients were assigned to one group, and female patients to another.

Statistical analyses were conducted with Student's *t* test and Pearson's correlation with the use of the Statistical Package for the Social Sciences (SPSS), version 11 (SPSS Inc., Chicago, Ill); data were shown as ±SD, and $P<.05$ was considered statistically significant.

RESULTS

Thirty seven (52.9%) of the 70 patients were men (group 1) and 33 (47.1%) were women (group 2), with a mean age (±SD) of 46.2±17.0 and 44.0±13.1 y, respectively. Mean duration of HD treatment was 33.0±26.0 mo for men and 33.7±8.5 for women. Demographic features, biochemical findings, and hematologic parameters of patients according to sex are shown in Table 1. BMD T scores in the osteopenia/osteoporosis range were observed at the LS in 58 patients (82.8%) and at the FN in 45 patients (64.3%). According to BMD measurements in the FN T score, 10% (n=7) of patients were osteoporotic, 54.3% (n=38) were osteopenic, and 35.7% (n=25) were normal; on the other hand, in terms of the LS T score, 47.1% (n=33) were seen to be osteoporotic, 35.7% (n=25), osteopenic, and 17.1% (n=12), normal. DEXA results of all patients are shown in Table 2. No statistically significant association was found in osteopenia/osteoporosis between sexes according to FN and LS T scores ($P=.542$ and $P=.267$, respectively); these results are detailed in Table 3. DEXA results of patients according to skeletal region are shown in Table 4.

Positive correlations between duration of HD and Kt/V, blood pH, and HCO_3 ($r=.224$, $P=.042$; $r=.249$, $P=.038$; $r=.266$, $P=.026$, respectively) were noted. A positive correlation was found between blood Ca levels and blood pH and HCO_3 ($r=.387$, $P=.001$; $r=.274$, $P=.022$, respectively). A negative correlation was found between levels of phosphorus and blood pH and HCO_3 ($r=-.290$, $P=.015$; $r=-.284$, $P=.017$, respectively), and between iPTH levels and HCO_3 ($r=-.260$, $P=.030$). A positive correlation was found between BMD T score of FN and patient age ($r=.413$, $P=.001$), and between iPTH and ALP levels ($r=.0408$, $P=.001$). No statistically significant relationship was observed between BMD and biochemical markers of bone turnover

(ie, between BMD and Ca, P, ALP, and iPTH). Pearson's correlation results are shown in Table 5.

Table 1. Demographic Features and Biochemical and Hematologic Parameters of Study Patients

Characteristics	Group 1 (n=37)	Group 2 (n=33)	*P* Value
Age, y	46.2±17.0	44.0±13.1	.554
HD duration, mo	33.0±26.0	33.7±28.5	.908
Kt/V	1.13±0.28	1.20±0.29	.316
Hct, %	31.5±4.5	30.3±4.8	.284
Albumin, g/dL	3.6±0.3	3.4±0.4	.029
Ca, mg/dL	9.1±1.3	8.6±0.9	.100
P, mg/dL	5.3±1.8	5.2±1.4	.730
CaXP, mg^2/dL^2	49.9±22.3	45.3±12.7	.310
iPTH, pg/mL	326.7±281.6	531.4±394.4	.014
ALP, mg/dL	115.7±67.2	131.0±75.0	.371
HCO_3, mmol/L	21.2±3.2	19.6±2.8	.025

Hct=hematocrit; CaXP=calcium × phosphate.

Table 2. DEXA Results for Individual Study Patients

T Score	T Score, Mean±SD	Z Score, Mean±SD	Normal Rate, %	Osteopenia Rate, %	Osteoporosis Rate, %
Femur neck	–1.27±0.87	–1.01±0.69	35.7	54.3	10.0
Lumbar spine	–2.32±1.32	–1.95±0.87	17.1	35.7	47.1

Table 3. DEXA Results for Study Groups

Characteristics	Group 1 (n=37)	Group 2 (n=33)	*P* Value
BMD in FN	0.84±0.12	0.84±0.15	.797
BMD in LS	0.81±0.16	0.85±0.17	.339
FN T score	–1.30±0.82	–1.23±0.93	.763
LS T score	–2.57±1.30	–2.03±1.29	.087

Table 4. DEXA Results of Study Patients by Group According to Skeletal Region

T Score	Femur Neck		Lumbar Spine	
	Group 1, n	Group 2, n	Group 1, n	Group 2, n
Normal (+1 or –1)	11	14	4	8
Osteopenia (–1 to –2.5)	22	16	13	12
Osteoporosis (≤–2.5)	4	3	20	13

Table 5. Results of Pearson's Correlation According to Skeletal Region

Parameters	Femur Neck		Lumbar Spine	
	r	*P* Value	*r*	*P* Value
Calcium	.102	.401	–.055	.650
Phosphorus	.176	.144	–.053	.661
Alkaline phosphatase	–.137	.257	.020	.867
iPTH	–.066	.590	–.029	.814

DISCUSSION

Renal osteodystrophy is a universal complication of uremia. These metabolic bone conditions have a wide spectrum ranging from secondary hyperparathyroidism to adynamic bone disease and osteoporosis.[6] Osteoporosis also may develop in patients with ESRD for many reasons beyond postmenopausal bone loss (in women) and age-related bone loss (in both sexes) and it is an important factor that increases morbidity in the HD population.[7,8] Patients with renal failure, especially those who are undergoing HD, are at high risk for low BMD and fracture because of associated risk factors, such as a sedentary lifestyle; the use of drugs such as heparin, corticosteroids, and immunosuppressants; acidosis; and uremic toxins.[6,9]

The diagnosis of osteoporosis in patients on HD is not as easy to confirm as it is in postmenopausal patients or in the normal population because, in the HD population, all forms of renal bone disease may cause fracture or result in low T scores.[10] Recent research has been conducted to explore new diagnostic, noninvasive methods and biochemical parameters for the diagnosis of osteoporosis in the ESRD population.[11-14] Zayour et al[12] reported the rate of osteoporosis as 55% in men and 87% in women undergoing HD; they suggested that sex, diabetes mellitus, and duration of HD were predictors of low BMD. In the present study, these rates were lower. According to BMD measurements in FN T score and LS T score, 10% and 47.1% of patients, respectively, were osteoporotic.

Fig 1. Comparison of T scores by patient sex.

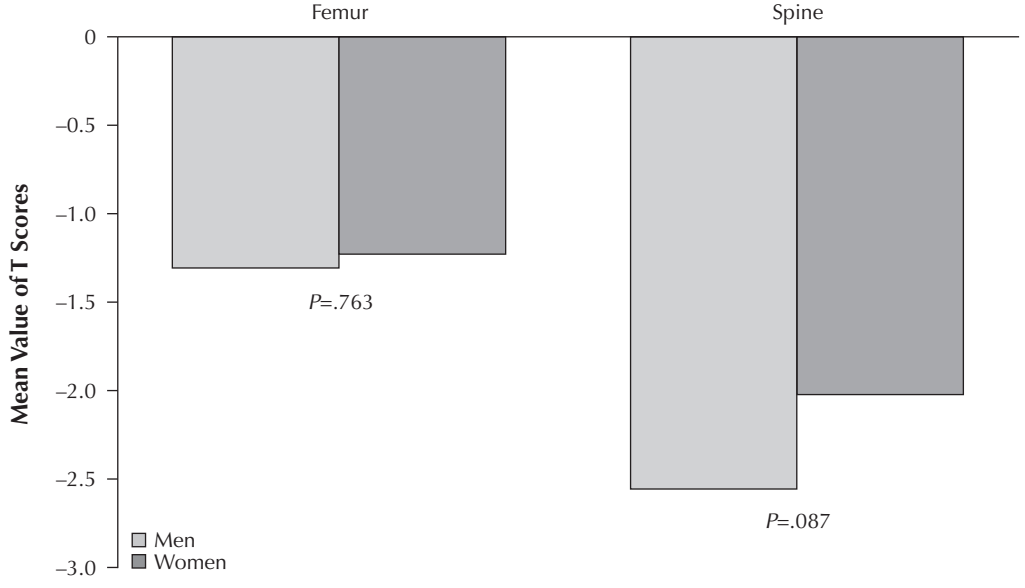
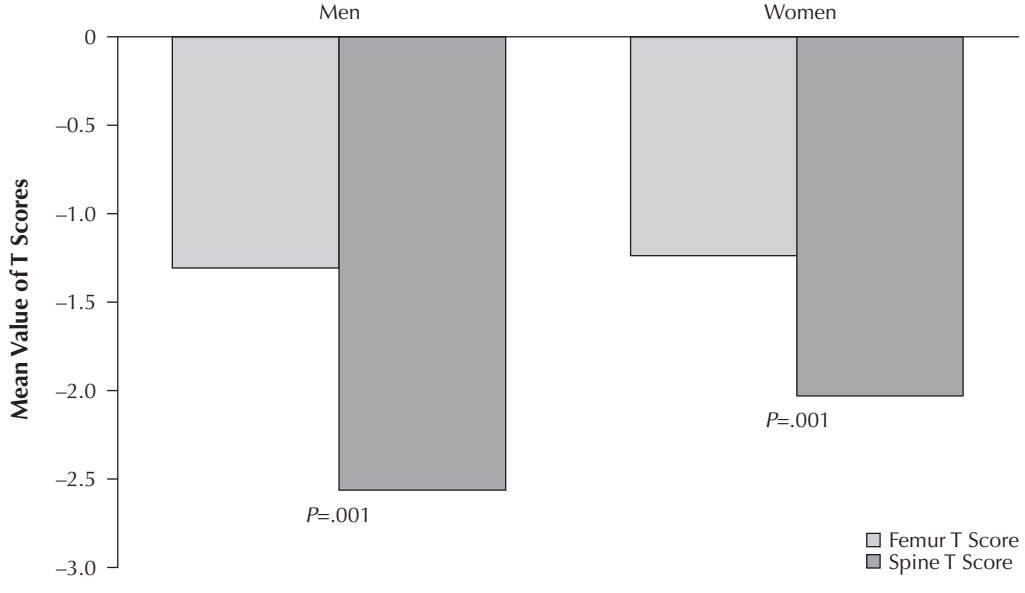


Fig 2. Comparison of femur and spine T scores by patient sex.



In contrast to the study of Zayour et al,[12] the current investigators found no statistically significant association in osteopenia/osteoporosis between the sexes, according to FN and LS T scores (P=.763 and P=.087, respectively) (Fig 1). A positive correlation was found, however, between the BMD T score of FN and patient age (r=.413, P=.000). These findings suggest that age is an important predictor of BMD in the HD population. In addition, the investigators found that patient LS T scores were generally worse than FN T scores (P=.001) (Fig 2).

Several studies have reported a negative association between iPTH levels with the use of a variety of measurements of BMD[7,15,16]; others have failed to show a negative association between iPTH levels and BMD.[17,18] Study data revealed no correlation between iPTH and BMD, and between BMD and other biochemical parameters, such as ALP, Ca, and P, that were used as predictors of renal osteodystrophy. The findings show that although these parameters are valuable predictors of renal osteodystrophy and cardiovascular complications in HD patients, they may not be useful for determining osteopenia/osteoporosis in this population. A positive correlation was found between iPTH and ALP levels (r=.408, P<.001). Although these 2 biochemical parameters are important markers of bone metabolism, elevated ALP levels combined with high iPTH levels may be predictive of renal osteodystrophy but not of adynamic bone disease/osteoporosis.

It is well known that chronic acidosis has adverse effects on bone metabolism in patients with ESRD.[19-22] Lemann et al[19] suggested that maintenance of acidosis relies on mobilization of bone minerals that causes a negative calcium balance; this negative balance results in bone demineralization, osteopenia, and fracture. In another study, Movilli et al[20] showed that correction of metabolic acidosis in HD patients reduces iPTH concentrations. Chronic acidosis in patients with ESRD contributes to renal osteodystrophy; together with hyperphosphatemia, hypocalcemia, and altered vitamin D metabolism, this may result in increased levels of iPTH. In keeping with these results, the investigators in the present study found a negative correlation between iPTH and HCO_3 levels (r=–.260, P=.030). Levels of iPTH were higher in patients with lower HCO_3 levels. A positive correlation was found between blood Ca levels and blood pH and HCO_3 (r=.387, P=.001; r=.274, P=.022, respectively). A negative correlation was found between levels of phosphorus and blood pH and HCO_3 (r=–.290, P=.015; r=–.284, P=.017, respectively). In addition to these correlations, another important positive correlation was noted between duration of HD and Kt/V, blood pH, and HCO_3 (r=.224, P=.042; r=.249, P=.038; r=.266, P=.026, respectively); this suggested the importance of dialysis adequacy for bone metabolism.

In conclusion, the investigators reported no correlation between markers of bone turnover and bone mass measurements in skeletal regions of the FN and the LS. LS T score results were worse than FN T score results. Correlations that were found between blood acidity parameters (pH, HCO_3) and elements, such as Ca and P, showed the importance of acid-base alterations in patients with chronic kidney disease, particularly HD patients. Elevated ALP levels combined with high iPTH levels are predictive of renal osteodystrophy but not of adynamic bone disease/osteoporosis. It should not be forgotten that osteoporosis occurs frequently among HD patients, and that the gold standard for diagnosis is DEXA—not the use of biochemical markers.

REFERENCES

1. Hruska KA, Teitelbaum SL. Mechanisms of disease—renal osteodystrophy. *N Engl J Med.* 1995; 333:166-174.
2. Ersoy FF. Osteoporosis in the elderly with chronic kidney disease. *Int Urol Nephrol.* 2007;39: 321-331.
3. Lobao R, Carvalho AB, Cuppari L, et al. High prevalence of low bone mineral density in predialysis chronic kidney disease patients: bone histomorphometric analysis. *Clin Nephrol.* 2004; 62:432-439.
4. Lacativa PG, de Mendonca LM, de Mattos P, et al. Risk factors for decreased total body and regional bone mineral density in hemodialysis patients with severe secondary hyperparathyroidism. *J Clin Densitom.* 2005;8:352-361.
5. Malluche HH, Monier-Faugere MC. The role of bone biopsy in the management of patients with renal osteodystrophy. *J Am Soc Nephrol.* 1994;4:1631-1642.
6. National Kidney Foundation. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis.* 2003;42:1-201.
7. Taal MW, Masud T, Green D, Cassidy MJ. Risk factors for reduced bone density in haemodialysis patients. *Nephrol Dial Transplant.* 1999;14:1922-1928.
8. Ersoy FF, Passadakis SP, Tam P, et al. Bone mineral density and its correlation with clinical and laboratory factors in chronic peritoneal dialysis patients. *J Bone Miner Metab.* 2006;24:79-86.
9. Urena P, Bernard-Poenaru O, Ostertag A, et al. Bone mineral density, biochemical markers and skeletal fractures in haemodialysis patients. *Nephrol Dial Transplant.* 2003;18:2325-2331.
10. Kullenberg R, Falch JA. Prevalence of osteoporosis using bone mineral measurements at the calcaneus by dual X-ray and laser (DXL). *Osteoporos Int.* 2003;14:823-827.
11. Hampson G, Vaja S, Evans C, et al. Comparison of the humoral markers of bone turnover and bone mineral density in patients on haemodialysis and continuous ambulatory peritoneal dialysis. *Nephron.* 2002;91:94-102.
12. Zayour D, Daouk M, Medawar W, Salamoun M, El-Hajj Fuleihan G. Predictors of bone mineral density in patients on hemodialysis. *Transplant Proc.* 2004;36:1297-1301.
13. Baszko-Blaszyk D, Grzegorzewska AE, Horst-Sikorska W, Sowinski J. Bone mass in chronic renal insufficiency patients treated with continuous ambulatory peritoneal dialysis. *Adv Perit Dial.* 2001;17:109-113.
14. Malyszko J, Brzosko S, Wolczynski S, Malyszko JS, Mysliwiec M. Bone metabolism in dialysis patients assessed by biochemical markers and densitometry. *Pol Arch Med Wewn.* 2003;110:967-972.
15. Yucel AE, Kart-Koseoglu H, Isiklar I, et al. Bone mineral density in patients on maintenance hemodialysis and effect of chronic hepatitis C virus infection. *Ren Fail.* 2004;26:159-164.
16. Coco M, Rush H. Increased incidence of hip fractures in dialysis patients with low serum parathyroid hormone. *Am J Kidney Dis.* 2000;36:1115-1121.
17. Jadoul M, Albert JM, Akiba T, et al. Incidence and risk factors for hip or other bone fractures among hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study. *Kidney Int.* 2006;70:1358-1366.
18. Ganesh SK, Stack AG, Levin NW, Hulbert-Shearon T, Port FK. Association of elevated serum PO(4), Ca × PO(4) product and parathyroid hormone with cardiac mortality risk in chronic hemodialysis patients. *J Am Soc Nephrol.* 2001;12:2131-2138.
19. Lemann J Jr, Bushinsky DA, Hamm LL. Bone buffering of acid and base in humans. *Am J Physiol Renal Physiol.* 2003;285:F811-F832.
20. Movilli E, Zani R, Carli O, et al. Direct effect of the correction of acidosis on plasma parathyroid hormone concentrations, calcium and phosphate in hemodialysis patients: a prospective study. *Nephron.* 2001;87:257-262.

21. Mathur RP, Dash SC, Gupta N, et al. Effects of correction of metabolic acidosis on blood urea and bone metabolism in patients with mild to moderate chronic kidney disease: a prospective randomized single blind controlled trial. *Ren Fail.* 2006;28:1-5.

22. Negri AL, Barone R, Quiroga MA, et al. Bone mineral density: serum markers of bone turnover and their relationships in peritoneal dialysis. *Perit Dial Int.* 2004;24:163-168.